IN THE CLAIMS:

Kindly amend the claims as follows:

Please amend claim 9 as shown in the attached pages entitled "Amended Claims for Attorney Docket Number LeA 32 545" (page 7 of this amendment). A marked version of the claim set showing the changes made is also attached (page 8 of this amendment).

Please add new claim 10 as shown in the attached pages entitled "New Claims for Attorney Docket Number LeA 32 545" (page 6 of this amendment).

REMARKS

Claims 9 and 10 are pending in this application. Claim 9 has been amended and new claim 10 has been added. These claim amendments and additions are made to clarify the subject matter therein. Therefore, these amendments are submitted in order to place the claims in condition for allowance, and do not disclaim any subject matter to which the Applicants are entitled.

Rejection Under 35 U.S.C. § 103(a)

In paragraph 6 (pages 2-3) of Paper No. 13, the Examiner rejected claim 9 under U.S.C. § 103(a) as unpatentable over Kruse et al., (1993) in view of Duschl, (1995). Applicants respectfully traverse.

To properly maintain a rejection under 35 U.S.C. § 103, three conditions must be met. First, the prior art must have suggested to those of ordinary skill in the art that they should make the claimed composition or device or carry out the claimed process. Second, the prior art must also have revealed that in so making or carrying out, those of ordinary skill in the art would have a reasonable expectation of success. Both the suggestion and the reasonable expectation of success must be adequately founded in the prior art and not in the Applicant's disclosure. Finally, the prior art reference must teach or suggest all the claim limitations. *See In re Vaeck*, 20 USPQ2d 1438, 1442 (Fed. Cir. 1991).

The Examiner stated:

> Kruse et al. teaches production of the muteins of IL-4 R121D, K123D, Y124D, S125D in *E.coli*. They measured receptor affinities of the variants are during competitive radioligand binding to Raji cells (Table1). However, Kruse et al. does not discuss the altered specificity of the muteins/variants.

> Duschl discloses the mutations in the IL-4 signaling site prevent association of γc, but not binding to IL-4Rα using conventional binding studies. This demonstrates that intact signaling site of IL-4 is required to recruit γc into the receptor complex (see abstract). Therefore, it would have been obvious to one of ordinary skill in the art, at the time the invention was made to analyze the muteins of the instant inventions as disclosed in Kruse et al. and Duschl et al. to study the change in affinity and specificity to various subunits, because Kruse et al. teaches that identifying the affinity and specificity will allow for rational design of high affinity IL-4 antagonist. Therefore, the instant invention is obvious over Kruse et al. (1993) in view of Duschl (1995).

As amended and claimed, the present invention relates to hIL-4 muteins having a reduced affinity and/or an altered specificity to the γ subunit of the IL-4 receptor and/or HIL-13 Rα subunit of the hIL-4 receptor, wherein one or more amino acids at positions 7, 11, 12, or 15 have been substituted with another amino acid (claim 9) and in addition, one or more amino acids substitutions at positions 121, 123, 124, or 125 (claim 10).

Kruse et al., does not teach or suggest the amino acids substitutions at positions 7, 11, 12, or 15; nor the combination of amino acids substitutions at positions 7, 11, 12, or 15 and substitutions at positions 121, 123, 124, or 125. In addition, Kruse et al. does not teach or suggest IL-4 muteins that have a reduced affinity and/or an altered specificity for the γ subunit. Kruse et al., states that IL-4 provides functionally distinct sites for interactions with receptor proteins, that is a "signalling site" and a "binding site" for IL-$4R_{ex}$ (the α subunit of the IL-4 receptor) (*see, eg.,* page 5125). In fact, Kruse et al., states that the "signalling site" is located in helix D and the "binding site" for IL-$4R_{ex}$ (the α subunit of the IL-4 receptor) is located in helices A and C. Thus, one skilled in the art would not be motivated to substitute amino acids at positions 7, 11, 12, or 15, located within the helix A, with the reasonable expectation of success, that is, producing an IL-4 mutein with a reduced affinity and/or an altered specificity for the γ subunit because helix A appears to be associated with the "binding site" for IL-$4R_{ex}$ (the α subunit of the IL-4 receptor).

The deficiencies of Kruse et al., are not remedied by Duschl. Duschl does not teach or suggest the amino acids substitutions at positions 7, 11, 12, or 15; nor the combination of amino acids substitutions at positions 7, 11, 12, or 15 and substitutions at positions 121, 123, 124, or 125. Similar to Kruse et al., Duschl states that helices A and C are associated with receptor binding. Furthermore, Duschl states that mutations of residues in helices A and C of IL-4 result in a loss of receptor binding (*see, eg.,* page 305). That is, these IL-4 mutants of helices A and C fail to bind to the α subunit of the IL-4 receptor. Thus, one skilled in the art would not be motivated to substitute amino acids at positions 7, 11, 12, or 15, located within the helix A, with the reasonable expectation of success, that is, producing an IL-4 mutein with a reduced affinity and/or an altered specificity for the γ subunit.

Since the combination of references does not teach every element of the claimed invention, these references cannot be combined to support a rejection of the claims under U.S.C. § 103(a). MPEP § 2143.

It is therefore respectfully submitted that Kruse et al., either singly or in combination with Duschl fail to teach or suggest the IL-4 muteins as presently claimed, and that the current invention is novel and nonobvious in view of the prior art references. For the foregoing reasons, Applicants respectfully request reconsideration and withdrawal of the present rejection.

CONCLUSION

For the foregoing reasons, Applicants submit that the claim is in condition for allowance and Applicants respectfully request reexamination of the present application, reconsideration and withdrawal of the present rejections and entry of the amendments. Should there be any further matter requiring consideration, Examiner Seharaseyon is invited to contact the undersigned counsel.

If there are any further fees due in connection with the filing of the present reply, please charge the fees to undersigned's Deposit Account No. 13-3372. If a fee is required for an extension of time not accounted for, such an extension is requested and the fee should also be charged to undersigned's deposit account.

Respectfully submitted,

November 13, 2002

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Amendment to Specification for Attorney Docket Number LeA 32 545

Amendment to Title:

Muteins of Interleukin 4 [showing low-affinity and short-term interaction with the common γ chain]

New Claims for Attorney Docket Number LeA 32 545

10. (New) An hIL-4 mutein according to claim 9, wherein one or more amino acids at position 121, 123, 124, or 125 have been substituted with another amino acid.

Amended Claims for Attorney Docket Number LeA 32 545

9. (Amended) An hIL-4 mutein having a reduced affinity and/or an altered specificity to the γ subunit of the IL-4 receptor and/or HIL-13 R α subunit of the hIL-4 receptor, wherein one or more amino acids at positions 7, 11, 12, or 15 have been substituted with another amino acid.

Amendments to the Claims (Attorney Docket No. Le A 32 545)
Version with Markings to Show Changes to Specification

9. (Amended) An hIL-4 mutein having a reduced affinity and/or an altered specificity to the γ subunit of the IL-4 receptor and/or HIL-13 R α subunit of the hIL-4 receptor, wherein one or more amino acids at positions 7, 11, 12, <u>or</u> 15[, 121, 123, 124, or 125] have been substituted with another amino acid.